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Psychiatric Disorder in a Familial 15;18 Translocation and Sublocalization of Myelin Basic Protein to 18q22.3

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Two related patients with similar clinical features consisting of a few dysmorphic signs and psychiatric disturbance were reported to have a partial trisomy of chromosomes 15(pter-q13.3) and 18(q23-qter) deriving from a familial translocation t(15;18). One patient is affected by bipolar disorder and the other by schizoaffective disorder. Both cases have a predominantly affective course; nevertheless, a clear diagnosis is difficult in the first patient, who is 15 years of age, and only a longitudinal course will allow us to establish a definite diagnosis. The possibility that these two pathologies belong to a single category is discussed, and the presence of a susceptibility locus on chromosome 18 is hypothesized. Cytogenetic data, FISH, and DNA studies indicate that the myelin basic protein (MPB) gene is not involved in the translocation, and localize it centromeric to the breakpoint on chromosome 18(q22.3). Thus, it is unlikely to be involved in the disease.

KEY WORDS: schizophrenia, affective disorder, chromosome 15, chromosome 18, translocation, myelin basic protein

INTRODUCTION

The genetics of major psychiatric illness have been intensively investigated. A strong genetic basis for both schizophrenia and affective disorder is clear, but a mendelian basis has not been established [Crow, 1990; Taylor, 1992; Craddock and McGuffin, 1993; Freedman et al., 1994]; and, to date, linkage studies have not been conclusive [Cloninger, 1994; Barr et al., 1994; Coon et al., 1994]. The concurrence of cytogenetic anomalies and major psychiatric disorders transmitted within the same family has been reported rarely [Bassett et al., 1988; Bassett, 1992; Blackwood et al., 1989; Gorwood et al., 1991; Garofalo et al., 1992; Seshadri et al., 1992; Mazida et al., 1993; Craddock and Owen, 1994]. Here we report a family in which a reciprocal translocation t(15;18) resulted in two unbalanced karyotypes with tertiary trisomy of chromosomes 15 and 18. Both affected subjects developed major psychiatric illness in their teens, consistently classified by two independent psychiatrists into two different entities according to the DSM-III-R criteria. The two cases have a predominantly affective course; nevertheless, a clear diagnosis is difficult in the first patient, who is only 15 years of age. This family may contribute to a possible localization for a major gene involved in psychiatric disorders.

Molecular characterization of the translocation allowed a more precise localization of myelin basic protein (MBP) on chromosome 18.

MATERIALS AND METHODS

Clinical Investigation

The two patients were seen by the same neuropsychiatrist (S.C.), and the diagnoses were confirmed by another psychiatrist blind to the research.

Case 1

K.M. is a 15-year-old girl, the first child of unrelated healthy parents. The mother had a previous spontaneous abortion and subsequently two healthy daughters. K.M. was born at term after an uneventful pregnancy

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Fig. 1. Proband: mild dysmorphic signs and obesity.

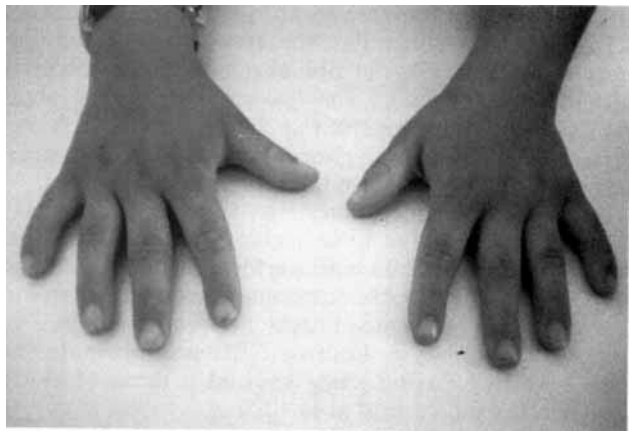

Fig. 2. Hands of patient showing brachydactyly and clinodactyly of fifth fingers.

and a normal delivery. Her psychomotor development was normal. She had menarche at 11 years of age; menses have always been very irregular.

At 3 years of age she attended a kindergarten, where she was described as shy. In primary school, she had difficulty separating from her mother, but her progress was fair. In secondary school, at 12 years of age, she was referred to a child psychiatrist because of some learning difficulties, and behavioural and speech problems. She started having some events of psychomotor agitation with insomnia, anorexia, logorrhea, and flight of ideas. These events occurred about twice a year and were well controlled by low doses of Tioridazina. Between these events K.M. showed a lack of interest, psychomotor retardation, hyperinsomnia, irritability, and social withdrawal. At 14 years of age, she had her first epileptic seizure with partially impaired consciousness and generalized tonic-clonic fit. During the following months, she had two more seizures. Carbamazepine, 500 mg twice a day, prevented other convulsive events.

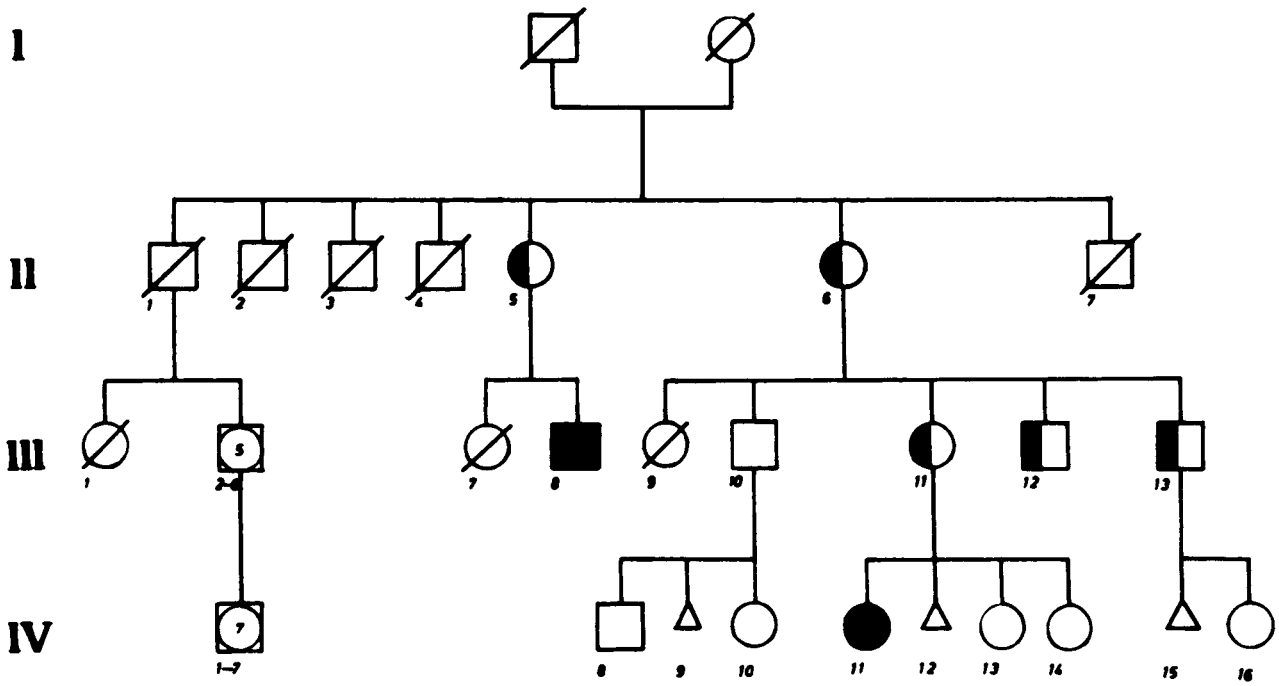

Fig. 3. Family pedigree: 47,XX,der(15),t(15;18)(q13.3;q22.3); 46,XX,t(15;18)(q13.3:q22.3).

At 15 years, her weight was 64 kg (>75 centile) and her height 152 cm (<10 centile). She showed some minor dysmorphic features (Fig. 1). She also had diffuse adiposity with stretch marks on the breasts and thighs, short hands due to short fingers (Fig. 2) (length of middle fingers: 6.5 cm, <3 centile), clinodactyly of the fifth fingers, and bilateral syndactyly of the second and third toes.

Neurological examination showed a bilateral Babinsky sign and hyperactive knee jerks. The WISC test revealed a total IQ of 83 with performance IQ of 68 and verbal IQ of 101. Routine examinations were normal.

A magnetic resonance imaging revealed only a septum Pellucidum cyst. Routine EEG was normal. The EEG recorded during sleep showed a focus of sharp waves in the left frontal area.

Her clinical history, together with interviews, Rorshach, and projective tests, led us to the diagnosis of a bipolar disorder with some psychotic aspects according to DSM-III-R criteria [1989].

Case 2

M.V. is a 49-year-old first cousin of K.M.'s mother (III-8, Fig. 3). His father is deceased; his mother is still alive and healthy. He was born at term after an uneventful pregnancy and a normal delivery. His psychomotor development was normal. After primary school, he was apprenticed to a carpenter. When he was 16, he had a period of psychomotor agitation, and delusional thoughts that led him to be admitted to a psychiatric hospital. He showed sudden delirium, insomnia, hyperactivity, and loghorrhea. This condition lasted 10 days and was followed by a period of depressed mood in which he was apathic and still had some delusional thoughts. In the following years he had several similar events complicated by visual and auditory hallucinations and two generalized tonic-clonic seizures. He received high doses of various neuroleptic and anticholinergic medications, as well as electroconvulsive therapy. The delusional thoughts increased, but he showed a progressive detachment from reality, and periods of excited mood were followed by periods of depressed mood. Since age 30 he has been living in a psychiatric unit.

Physical examination was normal, and the only dysmorphic feature is a thin helix. Neurological examination revealed a mild extrapyramidal rigidity. A CT scan showed a mild subcortical atrophy. His EEGs, which had been normal for many years, began to display a focus of slow waves in the right temporal area.

The diagnosis, according to the DSM-III-R, is schizoaffective disorder.

Cytogenetic Investigations

Peripheral blood lymphocytes were cultured, harvested, and banded according to standard procedures. Karyotypes of the patients and other family members (Fig. 4) were analyzed using GTG, CBG, DAPI, NOR, and QFQ conventional banding techniques.

Fluorescence In Situ Hybridization (FISH)

FISH was performed with D15S11 and GABRB3 biotinylated probes (ONCOR) specific for chromosome 15. Hybridization and post-hybridization washes for the two probes were carried out according to the ONCOR protocol. Detection was carried out according to the ONCOR detection kit with two amplification steps.

Chromosome 18 painting was performed with a whole chromosome 18-specific painting probe (ONCOR) following the kit supplier's instructions.

A minimum of 20 metaphases were examined in each hybridization experiment.

Molecular Studies

Genomic DNA from four family members (III-8, III-11, III-12, IV-11) was performed from peripheral blood using standard procedures.

The primer sequences for the tetranucleotide repeats region 5′ to the MBP gene were obtained from the sequence published by Boylan et al. [1990a,b]. MBP-1

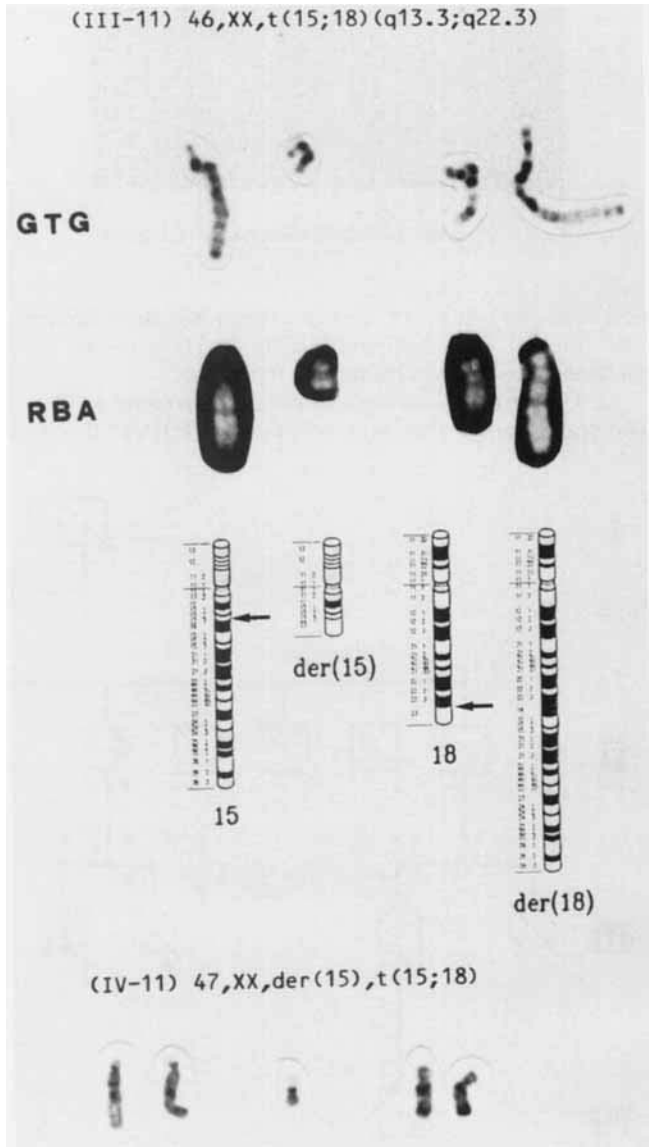

Fig. 4. Partial karyotype of the carrier and of trisomic patient. Below: ideograms of normal and translocated chromosomes 15 and 18.

was from the coding strand 5′GGACCTCGTGAATTACAATC3′ and recognized one binding site (bases 443–462); MBP-2 was from the complementary strand 5′ATTTACCTACCTGTTCATCC3′ and had two binding sites (bases 564–583;652–671) [Sajantila et al., 1992]. Target sequences were amplified [Saiki et al., 1988] in 25 μl reactions containing 100 ng of genomic DNA and 6.25 pmol of each oligonucleotide primer in 200 μm dNTP, 50 mM kCl, 10 mM Tris-HCl, pH 8.3, 1.5 mM MgCl2, 0.1% gelatin. One unit of Taq polymerase (Cetus Corp.) was added to each sample.

After 30 cycles (denaturation step 1 min at 94°C, annealing step 1 min at 52°C, and extension step 1 min at 72°C), there was an extension step of 10 min at 72°C. The amplified DNA samples were electrophoresed in a 10% polyacrylamide gel (40% acrylamide/2% bisacrylamide), and amplified alleles were detected by silver staining.

Peptidase A Enzyme Assay

The assay of peptidase A was performed according to the methods reported by Danesino et al. [1978].

RESULTS

Cytogenetics and FISH Studies

By G-banded chromosome analysis, family members II-5, II-6, III-11, III-12, and III-13 were detected carriers of a balanced translocation t(15;18)(q13.3;q22.3) (Fig. 4). This indicates that the probands (III-8 and IV-11) come from a segregation 3:1 during maternal meiosis, resulting in a partial trisomy of chromosomes 15(15pter-q13.3) and 18(q23). To complete the cytogenetic findings, metaphases from both subject III-11 and trisomic patient IV-11 were hybridized to chromosome 18 probe. In spreads from the III-11 carrier mother, fluorescence was observed on normal chromosomes 18 and on the additional chromosome (Fig. 5). In subject IV-11, the hybridization painted both normal chromosomes 18, and a signal was also present on the small supernumerary chromosome (Fig. 6). Hybridization of D15s11 and GABRB3 probes to metaphases of the trisomic patients showed signals both on normal chromosomes 15 and on the supernumerary chromosome (Fig. 7).

Molecular Studies

The tetranucleotide repeats regions to the MBP gene was investigated. Polymorphic loci were characterized by bands ranging from approximately 210 to 239 bp and from 115 to 135 bp in size, respectively (Fig. 8). Subjects III-11 and III-12 had identical polymorphic patterns (230/210 bp; 127/115 bp) and their trisomic cousin III-8 showed bands 210 bp and 119/115 bp in size. The polymorphic pattern of patient IV-11, compatible with inheritance from her mother (III-11), differed in all the allelic bands from that of patient III-8. Additional bands were present in subjects IV-11 (180 and 165 bp), III-11, and III-12 (180 bp).

Peptidase A Enzyme Assay

The assay of Peptidase A, whose gene is located on the terminal band of chromosome 18(q23) [Danesino et al., 1978] confirmed the partial trisomy of this chromosome. Peptidase A in trisomic patient IV-11 was 1.82 and in controls (n = 18) 0.94 ± 0.19.

DISCUSSION

Schizophrenia and related major mental illness are common in the general population (about 1%). Twin studies point to a major genetic contribution that is likely to be due to several different interacting genes. Cases of chromosomal abnormalities associated with neuropsychiatric problems have suggested regions in which there are genes predisposing to schizophrenia.

Fig. 5. Metaphases after FISH with whole chromosome 18 specific painting probe in a translocation carrier.

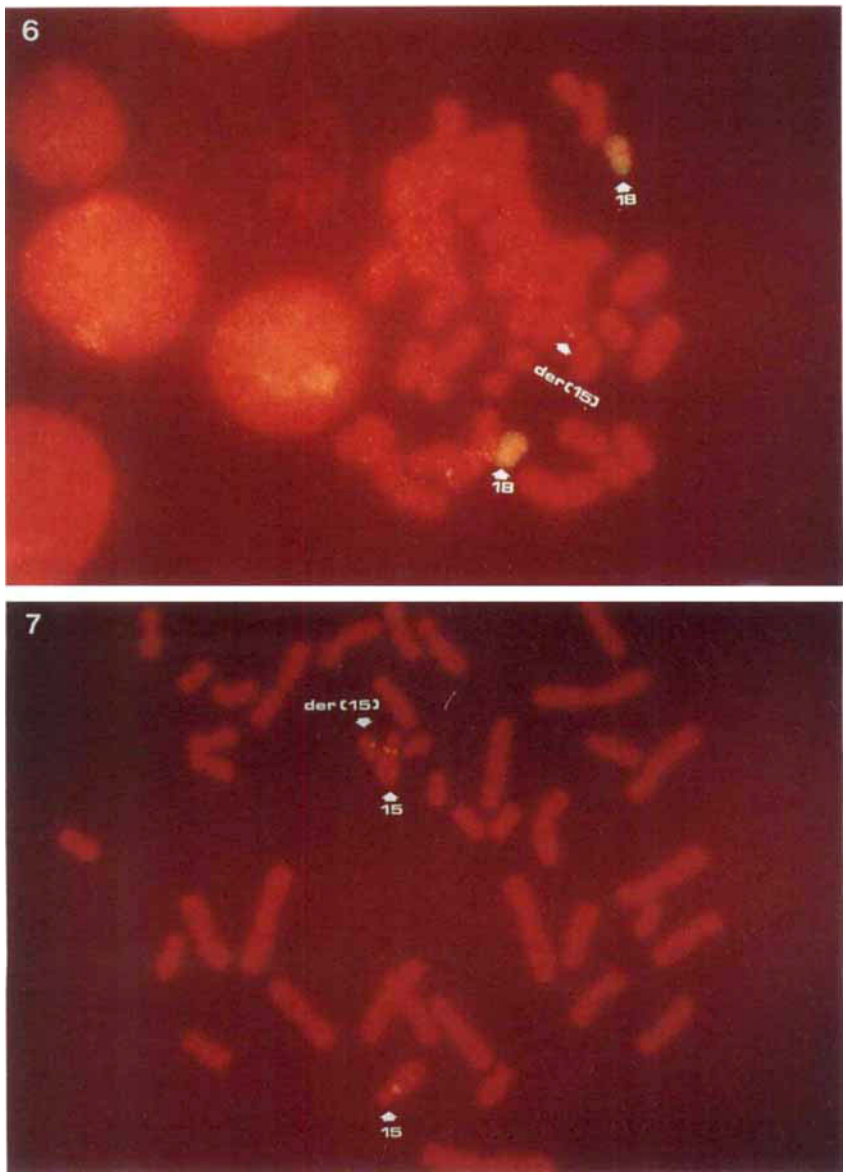

Fig. 6. Metaphases after FISH with whole chromosome 18 specific painting probe in a trisomic patient.
Fig. 7. Hybridization of D15S11 and GABRB3 probes to metaphases in a trisomic patient.

The two reported patients with the same unbalanced translocation involving chromosomes 15 and 18 are affected by conditions classified into different entities according to DSM-III-R criteria. The differentiation of psychosis associated with affective disorders from that associated with schizophrenia can be difficult, and sometimes only a longitudinal course (the girl is only 15 years old) allows us to establish a definitive diagnosis. The presence of major psychiatric illness in both of the karyotypically unbalanced patients is unlikely to be coincidental, especially considering the negative family history for psychiatric diseases.

Based on the segregation pattern of the chromosomal anomaly and pertinent family history of psychiatric illness, Bassett [1992] assessed criteria for relevance to localizing major genes for schizophrenia using standardized criteria for four areas (diagnosis, family history, specificity, and overall weight of evidence) with a range of scores from 0 to 3 for each. According to these criteria, our family achieved a score of 11 (probably high relevance).

Translocations involving chromosomes 15 and 18 have not been described.

Complete trisomies of chromosome 15 have been observed in spontaneous abortions [Kajii et al., 1973] and in a single liveborn who survived only a few days [Coldwell et al., 1981]. Cases of partial trisomy of the long arm of chromosome 15 have been described, both secondary to a balanced translocation [Bannister and Engel, 1975; Cohen et al., 1975; Power et al., 1977;

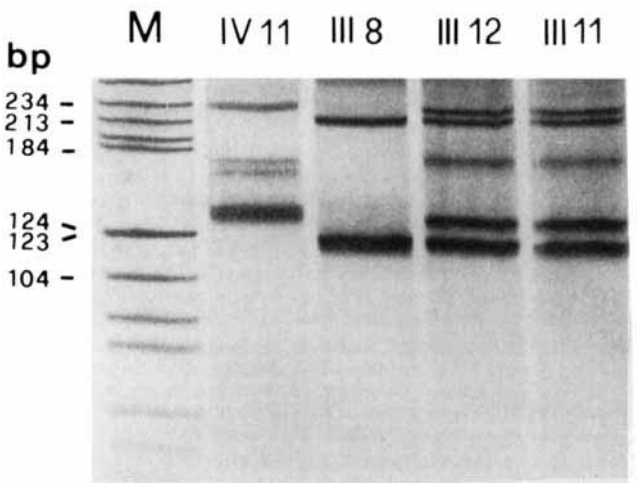

Fig. 8. Alleles of the STR region 5′ to the MBP gene separated by PAGE and silver stained. IV-11, III-8 trisomic patients; II-12, III-11: balanced translocation carriers. M, size marker, pBR 322 digested with HaeIII.

Wang and Hunter, 1979; Anneren and Gustavson, 1982; Kristofferson et al., 1987] and de novo [Parker et al., 1977; Hongell and Iivanainen, 1978; Veema et al., 1984; Herweijer et al., 1988]. No distinctive phenotype for partial trisomy 15 has been defined, although a severe mental and motor retardation with minor dysmorphic features and hypotonia seem to be constantly present [Robinson et al., 1991; Brookwell and Veleba, 1987; Turolla et al., 1989; Clayton-Smith et al., 1993]. Duplications involving the Prader-Willi region (15q11-13) have been associated with an obesity syndrome as well as with a normal phenotype [De France et al., 1984; Fuhrmann-Rieger et al., 1984; Pettigrew et al., 1987; Shohat et al., 1990].

Behavioural disturbance in patients with abnormalities of chromosome 15q11-12 have been reported [Smith and Einfeld, 1986; Schinzel, 1981]. Moreover, autistic disorder has been associated with partial trisomy or tetrasomy of chromosome 15 [Schinzel, 1990; Gillberg et al., 1991].

Our case 1, trisomic for the chromosomal region 15q11-q13, presents some signs (behavioural disturbance) similar to those found in patients with so-called inv dup(15)(pter-q13) [Schinzel, 1990], and others (short stature, obesity, acromicria) typical of Prader-Willi syndrome. Nevertheless, behavioural problems and mental retardation present in Prader-Willi and Angelman syndromes are not consistent with the psychiatric diagnoses of our patients.

On chromosome 15, in the same region involved in the translocation, was localized the nicotinic receptor gene, a possible susceptibility locus for schizophrenia [Freedman et al., 1994].

A few cases of partial distal trisomy 18q have been reported in the literature [Murthy et al., 1980; De Muelenaere et al., 1981; Wilson et al., 1990; Mewar e t al., 1993]. Unlike our patients, these cases had growth delay, mental retardation [De Muelenaere et al., 1981; Matsuoka et al., 1981; Wilson et al., 1990; Kline et al., 1993], but lacked specific dysmorphic features.

Both Bassett [1992] and Craddock and Owen [1994] report bipolar patients with a ring chromosome 18, with approximate deleted segment at 18pter-p11 and also at 18q23-qter. Bassett also reports a balanced translocation (2q21;18q23) in a schizophrenic patient and behavioural problems in one of his daughters.

In a study of families affected by bipolar schizoaffective disorder, a potential linkage with chromosome 18 was found by Van Kessel et al. [1994], and a positive lod score suggesting a linkage was found in the de Bruyn study [in press]. Coon et al. [in press] found a maximum lod score of 2.22 for a marker localized to 18q23, and other markers were also positive in this region.

The data in the literature and those obtained from our study family allow us to hypothesize the presence of a gene for susceptibility to bipolar illness on the terminal part of 18q even if the existence of a susceptibility locus for schizophrenia on chromosome 15 does not allow us to exclude a role of this chromosome.

The comparison between the inheritance of the translocated chromosome and of markers offers the opportunity for a precise gene localization. The MBP gene is close to the breakpoint and, in addition, contains new informative polymorphisms. DNA from the two related patients and other members of their family were employed to sublocalize the MBP gene by means of molecular studies. The completely different patterns observed in the two related affected patients show that the MBP gene is not involved in the translocation, thus indicating that it is unlikely to be involved in the etiology of manic depression. Considering the case published by McGinniss et al. [1993] and the mapping of chromosome 18 [Saxe et al., 1985; van Kessel et al., 1994; Muleris et al., 1994], it is possible to localize the proximal-distal sequence for the marker 18D211 and MBP in the q22.3 band of chromosome 18.

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